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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.   | CONFIRMATION NO. |
|--|-------------|----------------------|-----------------------|------------------|
| 09/804,700   | 03/13/2001  | Robert D. Ladner     | 266/176               | 1989             |
| 34055  | 7590        | 02/23/2004           | EXAMINER              |                  |
| PERKINS COIE LLP<br>POST OFFICE BOX 1208<br>SEATTLE, WA 98111-1208 |             |                      | CHUNDURU, SURYAPRABHA |                  |
|  |             |                      | ART UNIT              | PAPER NUMBER     |
|  |             |                      | 1637                  |                  |

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 09/804,700             | LADNER ET AL.       |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Suryaprabha Chunduru   | 1637                |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 September 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,5-8 and 13-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-8 and 13-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date. _____  | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

1. Applicants' response to the office action and amendment filed on September 5, 2003 has been entered.
2. Claims 1,3 and 5-7 are amended. Claims 4 and 9-12 are cancelled. Claims 13-25 are added. Thus claims 1-3, 5-8, 13-25 are pending.
3. This application is filed on March 13, 2001 and claims priority to a provisional application filed on March 15, 2000.

***Response to Arguments***

4. Applicant's response to the office action (Paper No.8) is fully considered and is found persuasive.
5. With respect to the rejections made in the previous office action under 35 U.S.C. 103(a) over Ladner et al. in view of Lundquist et al. and Ladner in view of Lundquist et al. further in view of Pearlman et al. ., applicants amendment and arguments have been considered but are moot in view of the new ground(s) of rejection.

***New Grounds of Rejections Necessitated by Amendment***

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1637

Claims 1-3, 5-8, 13-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Ladner (USPN. 5,962,246) in view Beck et al. (Adv. Exp. Med. Biol., Vol. 195, pages 97-104, 1986).

Ladner et al. teach a method of claims 1, 13, 22, 23, for determining if a test compound (s) induces uracil misincorporation into DNA (see column 9, lines 7-27), wherein Ladner et al. teach that the method comprises

(a) providing normal or wild type cells (resting or non-proliferative cells (low dUTPase levels) or proliferating cells (high or over expressing dUTPase) (see column 9, lines 64-67, column 10, lines 1-6);

(b) exposing or treating the cells to an agent that inhibits thymidylate metabolism (see column 9, lines 13- 27, column 12, lines 32-48);

(c ) measuring cell growth or proliferation or viability or measuring incorporation of uracil (dUTP) or amount of dUTPase (see column 10, lines 7-21, column 12, lines 26-48, column 10, lines 44-46);

(d) and interpreting the measured features wherein presence or absence of uracil in DNA in each of the cell types is indicative of the test compound inducing uracil misincorporation into DNA (see column 12, lines 26-48) and involvement of dUTPase in cell cycle checkpoint arrest (cyclin dependent kinase phosphorylation) (see column 8, lines 50-56) and determining sensitivity or resistance of a test compound (see column 9, lines 13-45).

With regard to claims 2-3, 5-6, Ladner et al. also teach that the cells over expressing a dUTPase are selected from organism including yeast, viruses (see column 8, lines 57-67, column 9, lines 1-6), humans, animals, plants, fungi, bacteria and viruses (see column 10, lines 22-30);

Art Unit: 1637

With regard to claims 14, 15, Ladner et al. teach that the method comprises one or more test compounds (see column 9, lines 13-27);

With regard to claim 16-17, Ladner et al. also teach that the test compound is an antifolate agent (antineoplastic or antiparasitic agents) (see column 9, lines 13-45);

With regard to claim 18, Ladner et al. teach that the method comprises cells from the same species (see column 10, lines 38-43);

With regard to claim 19, Ladner et al. teach that the cells are from human cells (see column 10, lines 22-30);

With regard to claims 20-21, 24-25, Ladner et al. also teach that the method is used to screen compounds for treatment of human disease, cancer (see column 9, lines 13-45)

However with reference to claims 1, 7-8, 13, 22, 23, Ladner et al. did not teach use of cell types expressing uracil-DNA glycosylase.

Beck et al. teach a method for screening cytotoxic agent (methotrexate) and uracil analogues that affect uracil misincorporation, wherein Beck et al. discloses that the method comprises (i) assaying the dUTPase and uracil-DNA-glycosylase (UNG) levels in various cell lines (see page 97, paragraph 1 in Results section) (ii) correlating test compound resistance with dUTPase levels by analyzing dUTPase, UNG, cell growth and uracil misincorporation (see page 101, paragraph 1) and implicating that the inhibition of dUTPase activity elevates dUTP levels and enhance misincorporation of uracil into DNA and cytotoxicity (see page 103, paragraph 1); Beck et al. also teach that the method comprises inhibitor of uracil-DNA glycosylase (see page 98, lines 3-6, Fig. 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of determining uracil misincorporation into DNA as taught by Ladner et al. with the various cells expressing/or inhibiting uracil-DNA glycosylase as taught by Beck et al. to achieve expected advantage of developing a sensitive method for characterizing uracil misincorporation into DNA because Beck et al. taught that association of thymineless state increases intracellular dUTP and dUMP levels with resulting uracil misincorporation into DNA and subsequent unrepaired excisions of uracils by uracil-DNA glycosylase lead to DNA fragmentation. An ordinary practitioner would have been motivated to combine the method of Ladner et al. with the method of Beck et al. to enhance the sensitivity of the assay by incorporating the additional parameters to support the uracil misincorporation into DNA because in addition to measuring dUTPase and dUTP levels, incorporation of the parameter UNG+ and UNG- cells would result in a better profile for characterization of a test compound and its role in misincorporation of uracil into DNA.

### ***Conclusion***

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period


Art Unit: 1637

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

  
Suryaprabha Chunduru  
February 19, 2004

  
**JEFFREY FREDMAN**  
**PRIMARY EXAMINER**